PATENT SPECIFICATION (11) 1 527 638

1 527 638

(21) Application No. 52104/76 (22) Filed 14 Dec. 1976
(31) Convention Application No. 2557615
(32) Filed 20 Dec. 1975 in
(33) Federal Republic of Germany (DE)
(44) Complete Specification published 4 Oct. 1978
(51) INT CL² A61K 31/165 47/00
(52) Index at acceptance
A5B 26Y 281 28Y 341 342 343 34Y 38Y 391 480 482 48Y 490 493 49Y 542 54Y 566 56Y 586 58Y 646 64Y 754 75Y

(19)

(72) Inventors KURT BAUER
KARL ERNST FETTING
RUDOLF GONNERT
HERBERT THOMAS and
HERBERT VOEGE

(54) NEW NICLOSAMIDE SUSPENSION FORMULATIONS

(71) We, BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of Leverkusen Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to formulations of niclosamide and of its salts suitable for medical administration.

Formulations of 2-hydroxy-5-2'-dichloro-4'-nitrobenzanilide (herein referred to as "niclosamide"), which is a substance having an anthelmintic action, and of its salts (in particular of the piperazine salt) have already been disclosed.

In this context it should be pointed out that niclosamide and its salts have hitherto generally been used as tablets and, particularly in veterinary medicine, as so-called "wettable powders".

A "wettable powder" (abbreviation: WP) is understood as a powder which, before it is used, can easily be stirred in water to give a homogeneous, ready-to-use suspension.

In the formulations previously known, the active compound niclosamide and its salts are generally employed in a micronised form (in this case, the maximum in the particle size distribution curve is between 2 and 50 μ and especially between 2 and 20 μ).

However, the previous formulations of niclosamide and of its salts had the disadvantage that they were either not immediately ready for use (wettable powders) and/or that a relatively large dose was necessary in order to achieve the same activity (tablet/wettable powders).

It has not yet been possible hitherto to prepare stable formulations of niclosamide and of its salts with a more finely ground or precipitated active compound (particle size about 1 μ) in an aqueous medium. This is because it has been found, in general, that an undesirable growth in the particle size of the niclosamide or niclosamide salt particles takes place after a relatively short time and this prevents good resorption of the active compound. Thus, all commercially prepared aqueous suspension formulations exhibit crystals of 20 μ and larger. This growth in the particle size has been found hitherto when anhydrous niclosamide and niclosamide containing water of crystallisation, and also the niclosamide salts, were used.

According to the present invention we provide an oil-based suspension of niclosamide, or a salt thereof, in which at least 50 per cent of the particles of the niclosamide or its salt are smaller than 2 μ. Preferably at least 50 per cent of the particles of niclosamide or its salt are smaller than 1 μ.

The formulations of the invention display a particularly high anthelmintic activity and have a very high stability.

In this context it should be mentioned that resorption of the medicament from suspensions which are prepared with oily solvents can be improved or impaired, compared with that from an aqueous suspension.

Thus, for example, it has been reported that in the case of griseofulvin a corres-

ponding oily suspension of the active compound gives better plasma concentrations of the active compound than does an aqueous suspension (see P. J. Carrigan and T. R. Bates, I. Pharm. Sci. *62* (9), 1,476 (1973).

On the other hand, experiments showed that in m st cases lower plasma concentrations of the active compound are obtained with an oily suspension, that is to say the resorption of the active compound which takes place is poorer than in the case of aqueous suspensions (in this context see, for example, Untersuchungen beim Ampicillin (Experiments with Ampicillin) K. Bauer, Rheinisches Ärzteblatt No. 5/1975).

On the basis of the above, it is therefore to be regarded as surprising that the active compound niclosamide and its salts have such a good action in oily suspension and that finer grinding results in an improvement in the activity and, above all, the stability, these improvements being distinctly superior to those achieved with the micronised aqueous use form employed hitherto.

The invention also provides a method of combating (including the prevention relief or cure of) intestinal infection in non-human animals which comprises administering to the animals a suspension according to the invention.

The active compound which is used according to the invention, that it to say niclosamide (2-hydroxy-5,2'-dichloro-4'-nitrobenzanelide) and its use as an anthelmintic, especially as an agent for combating tapeworms, are, as has been stated, already known (see, for example, British Patent Specification No. 889,377). Moreover, salts of niclosamide and their use as anthelmintics are already known (with regard to the piperazine salt of niclosamide see, for example, German Patent No. 1,194,866, French Patent No. 1,509,908 and British Patent No. 966,074).

The formulations according to the invention comprise the active compound (niclosamide or a niclosamide salt), oily liquid excipients and, optionally, surface-active agents or emulsifiers.

The following can be used as the active compounds: anhydrous niclosamide, niclosamide containing water of crystallisation, and niclosamide salts, especially the piperazine salt of niclosamide.

The preferred oily liquid excipients are physiologically acceptable oily liquid excipients in which the active compound is virtually insoluble. The following compounds are preferably employed according to the invention as liquid excipients: liquid paraffins, vegetable oils, for example, sesame oil, groundnut oil, cotton seed oil, sunflower oil or olive oil, synthetic or partially synthetic oils, such as triglycerides of capric/caprylic acid, mixtures of triglycerides of saturated vegetable fatty acids of medium chain length, esters of fatty acids with fatty alcohols, such as oleic acid oleyl ester and oleic acid decyl ester, esters of a branched fatty acid of medium chain length with saturated fatty alcohols (C_{16}—C_{18}) and ethyl stearate. Further solvents, such as, for example, alcohols, (such as n- or iso-propanol, n-butanol or t-butanol) are optionally also added.

Examples of surface-active agents (comprising emulsifiers and wetting agents and frequently substances which at the same time promote resorption) are:

1. anionic surface-active agents, such as Na laurylsulphate, fatty alcohol ether sulphates and monoethanolamine salts of mono-/di-alkyl-polyglycol-ether-orthophosphoric acid esters,
2. cationic surface-active agents, such as cetyltrimethylammonium chloride,
3. ampholytic surface-active agents, such as di-Na N-lauryl-β-iminodipropionate or lecithin, and
4. non-ionic surface-active agents, for example polyoxethylated castor oil, polyoxyethylated sorbitan monooleate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate and alkylphenol polyglycol ethers.

The formulations according to the invention preferably contain the active compound (niclosamide or a niclosamide salt) in concentrations of from 2 to 60 per cent (weight/volume) and most preferably from 5 to 20 per cent (weight/volume).

The suspension formulations according to the invention preferably contain the liquid excipients in an amount of from 20 to 98 per cent (weight/volume) and preferably of from 80 to 95 per cent (weight/volume).

The suspension formulations according to the invention preferably contain the surface-active agents (comprising emulsifiers and wetting agents) in an amount of from 0 to 30 per cent (weight/volume) and most preferably of from 1 to 20 per cent (weight/volume).

The auxiliaries according to the invention (liquid excipients and surface-active agents) are generally employed in the pure form for the preparation of the suspension formulations according t the invention.

In order to prepare the suspension formulations according to the invention, the active compound (anhydrous niclosamide, niclosamide containing water of crystallisation, or a niclosamide salt, especially the piperazine salt of niclosamide) is ground in the oily liquid excipient to the required particle size in a manner which is in itself known e.g. using ball mills, stirred ball mills or other suitable comminuting apparatus.

Preferably, in the process according t the invention, a so-called preconcentrate in which appr ximately 50 per cent of the particles should be ground to smaller than 2 μ and preferably smaller than 1 μ is first prepared.

A surface-active agent (wetting agent and/or emulsifier) is optionally added to this preconcentrate.

The concentrate which is now obtained is then preferably diluted with the liquid excipient to the desired use concentration.

The preferred sequence of process steps described above does not have to be strictly maintained. The sequence of process steps can be varied to a substantial extent. Moreover, it is also possible to employ a mixture of liquid excipients and/or surface-active agents for the preparation of the suspension formulations according to the invention.

The suspension formulations according to the invention are used in the same way as the previously known formulations of the same active compound (niclosamide or a salt of niclosamide) which has an anthelmintic action and, in particular, an action against tapeworms.

It is intended to demonstrate the preparation of the suspension formulations according to the invention by means of the examples which follow. However, these examples are intended to show only a few possibilities for the preparation of the suspension formulations according to the invention and not to have a restrictive effect. The symbol ® designates a Registered Trade Mark.

Example 1

A 20% w/w concentrate of niclosamide containing water of crystallisation in paraffin of low viscosity is ground, in a high-speed stirred ball mill (for example of the Uni-mill, bead-mill or sand mill type) to a particle size such that about 50% of the particles are smaller than 1 μ. Glass Beads with a diameter of 318—418 μ are employed as the grinding aid. 0.5% of lecithin is added as the wetting agent. A 4% niclosamide weight/volume suspension in paraffin of low viscosity with a lecithin content of 3% is prepared from this concentrate by diluting with said paraffin and adding lecithin. A read-to-use stable suspension which can be administered easily results.

Example 2

In the same way as in Example 1, a 20% strength suspension of niclosamide in sesame oil is ground. The concentrate is diluted to 10% niclosamide content with sesame oil, with the addition of 5% of polyoxyethylene-sorbitan monooleate and 10% of n-butanol.

The formulation can be administered easily and in the case of moniezia infection of sheep is effective in a dose of 35 mg/kg. This is about half of the dose of niclosamide which is otherwise customary.

Example 3

A niclosamide concentrate is prepared in the manner described in Example 1. After adding 5% of polyoxyethylene-sorbitan monooleate, it is diluted to 10% weight of niclosamide/volume with liquid paraffin of low viscosity.

The biological activity of the suspension formulations according to the invention was tested, compared with that of the previously known formulations of the same activity compound.

In order to compare the activity of the formulation of Example 1 with that of a known formulation, an identical 4% strength suspension in which the mixmum in the particle size distribution was at about 5 μ was prepared.

Example A

Hymenolepsis nana—mice

Animals infected experimentally with Hymenolepsis nana were treated orally after the prepatent period of the parasites had elapsed. The degree of efficacy of the formulation is determined by counting, after dissection, the worms which remained in the test animal, compared with the number of untreated control animals, and then calculating the percentage action.

niclosamide in water insoluble

Table relating to Example A

Preparation/formulation	Daily dose of active compound in mg/kg	Reduction in parasites in per cent
Oily suspension (liquid paraffin) of sand mill-ground niclosamide	500	100
	250	100
	100	96
Suspension of sand mill-ground niclosamide in liquid paraffin, with the addition of 0.5% of lecithin, according to Example 1	500	100
	250	100
	100	93
Suspension of sand mill-ground niclosamide in liquid paraffin, with the addition of 0.5% of polyoxyethylated sorbitan monooleate (Arlacel L®), prepared analogously to Example 3	500	100
	250	99
	100	94
Suspension of sand mill-ground niclosamide in liquid paraffin, with the addition of 3% of polyoxyethylated sorbitan monooleate (Arlacel L®), prepared analogously to Example 3	500	100
	250	100
	100	93
Untreated controls	—	0

Table relating to Example A

For comparison: tests with micronised niclosamide active compound (particle size distribution maximum about 5 μ).

Preparation/formulation	Daily dose of active compound in mg/kg	Reduction in parasites in per cent
Oily suspension (liquid paraffin) of micronised niclosamide	500	61
	250	23
	100	16
Suspension of micronized niclosamide in liquid paraffin with the addition of 5% of lecithin	500	94
	250	66
	100	34
Suspension of micronised niclosamide in liquid paraffin with addition of 3% of lecithin	500	99
	250	91
	100	47
Suspension of micronised niclosamide in liquid paraffin with the addition of 0.5% of polyoxyethylated sorbitan monooleate (Arlacel L®)	500	76
	250	49
	100	0
Suspension of micronised niclosamide in liquid paraffin with addition of 3% of polyoxyethylated sorbitan monooleate (Arlacel L®)	500	66
	250	40
	100	16
Untreated controls	—	0

Example B

Taenia hydatigena/dogs

Dogs infected experimentally with Taenia hydatigena were treated after th prepatent period of the parasites had elapsed. The active compound was administered orally. The degree of efficacy of the formulation employed was determined by counting, after dissection, the worms which remained in the test animal, compared with the number in untreated control animals, and also by determining the number of parasite-free dogs relative to the total number of d gs treated with the particular dose and also by determining the average number of parasites per dog.

Table relating to Example B

Formulation	Dose in mg/kg	Number of parasite-free dogs/ total number of dogs	Average number of parasites per dog
Piperazine salt of niclosamide in pulverulent form (particle size distribution maximum about 5 μ)	2.0	5/10	0.8 (0—2)
	4.0	7/10	0.4 (0—2)
	8.0	8/10	0.4 (0—2)
	16.0	10/10	0
	32.0	10/10	0
Sand mill-ground niclosamide suspended in liquid paraffin, according to the invention	0.25	3/10	1.3 (1—4)
	0.5	6/10	0.7 (1—3)
	1.0	7/10	0.5 (1—2)
	2.0	10/10	0
	4.0	10/10	0
Untreated controls	—	0/20	3.6 (1—4)

WHAT WE CLAIM IS:—

1. An oil-based suspension of niclosamide (2-hydroxy-5-2'-dichloro-4'-nitrobenzanilide) or a salt thereof in which at least 50% of the particles of the said compound are smaller than 2 μ.

2. A suspension according to claim 1 wherein the said compound is in its anhydrous form.

3. A suspension according to claim 1 wherein the said compound is in a form which contains water of crystallisation.

4. A suspension according to claim 1, wherein the said compound is in the form of a piperazine salt.

5. A suspension according to any one of claims 1 to 4 including a surface-active agent.

6. A suspension according to claim 5 wherein the surface active agent comprises lecithin or a polyoxyethylated sorbitan monolaurate.

7. A suspension according to claim 5 or claim 6 including up to 30% (weight/volume) of the surface active agent.

8. A suspension according to any one of claims 1 to 7 wherein the oil base comprises a liquid paraffin or sesame oil.

9. A suspension according to any one of claims 1 to 8 comprising from 2 to 60% (weight/volume) of the said compound.

10. A suspension according to any one of claims 1 to 9 wherein at least 50% of the particles of the said compound are smaller than 1 μ.

11. An oil-based suspension substantially as hereinbefore described in any one of Examples 1 to 3.

12. A process for the preparation of a suspension according to any one of claims 1 to 10 wherein anhydrous niclosamide, niclosamide containing water of crystallisation, or a niclosamide salt is ground in an oily liquid excipient, to an extent such that at least 50 per cent of the particles of active compound are smaller than 2 μ.

13. A process according to claim 12 wherein a surface-active agent is added to the suspension after grinding.

14. A process according to claim 12 or claim 13 wherein the suspension is further diluted with the liquid excipient to a desired concentration.

15. A process for the preparation of an oil-based suspension containing niclosamide according to claim 1 substantially as hereinbefore described in any one of the Examples.

16. An oil-based suspension of niclosamide when prepared by a process according to any one of claims 12 to 15.

17. A method of combating intestinal infection in non-human animals which comprises administering to the animals a suspension according to any one of claims 1 to 11 and 16.

For the Applicants
CARPMAELS & RANSFORD
Chartered Patent Agents
43 Bloomsbury Square
London, WC1A 2RA.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1978
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

See GB 2222770